Pertanika J. Sci. & Technol. 27 (4): 1509 - 1525 (2019)

PERTANIKA JOURNALS

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

Review article

Timing and Prognostic Factors of Tuberculosis Treatment Interruption

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ABSTRACT

The global Tuberculosis epidemic (TB) poses a significant public health threat. While the consequences of TB treatment interruption are indisputable, the knowledge about the timing and prognostic factors of TB treatment interruption is fundamental. Despite a considerable amount of evaluation, the timing and prognostic factors of TB treatment interruption have been inconsistently identified from one study to another. Therefore, this study aimed to examine the evidence obtained from published literature on the timing and prognostic factors of TB treatment interruption at different points of the treatment course. In this review, three databases namely *Pubmed, Scopus*, and *Science Direct* were used to identify articles published from January 2003 to February 2018. This was based on the inclusion criteria and keywords including 'default', 'survival time', 'tuberculosis', and 'treatment interruption'. The nine selected studies were prospective and retrospective cohort studies conducted in developing countries. The diversity of the study's participants and TB treatment interruption definition were allowed, thus delineating a heterogeneous finding. This review suggests that the interruption predominantly occurred during the maintenance phase of treatment course. Despite the finding, a considerable gap in understanding the prognostic factors at different time points of TB treatment interruption was elicited. The heterogeneity across the studies may limit the inferences and warrant further evaluation. In essence,

ARTICLE INFO

Article history:
Received: 02 July 2018
Accepted: 13 May 2019
Published: 21 October 2019

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ISSN: 0128-7680
e-ISSN: 2231-8526

the time-related information should be integrated into framing impactful public health strategy, while a vigorous attempt on the evaluation of the cognitive, behavioural and psychosocial aspects may be beneficial.

Keywords: Default, survival time, treatment interruption, tuberculosis

INTRODUCTION

The 20th century has demonstrated a significant public health threat posed by the re-emergence of an ancient airborne disease which is Tuberculosis (TB). The TB mortality has been substantial, reaching approximate 1.6 million in 2016, while the slow falling rate of TB incidence has been illustrated across the nations (World Health Organization, 2017). This has called for an intensified global effort to end TB global epidemic via End TB strategy. As one of the major obstacles in successfully treating 85% of the detected TB cases, TB treatment interruption should be the focus area of improvement in TB management (World Health Organization, 2017).

TB treatment interruption is defined as a history of stopping treatment for two or more consecutive months (World Health Organization, 2014). Evidently, TB treatment interruption has led to devastating consequences including delayed sputum conversion, drug resistance, longer treatment regimes, incomplete treatment, hence collectively exhibit prolonged infectiousness to the community (Dominguez-Castellano et al., 2003; Kuaban et al., 2009; Marx et al., 2012; Nahid et al., 2011; Pablos-Méndez et al. 1996; Vree et al., 2007). Importantly, TB treatment interruption has also posed significant economic burden and dependency through increased hospital admission and bed occupancy, thus leading to significant psychosocial impact (Cerdá et al., 2014; Pettit et al., 2013).

The recent two decades have demonstrated vigorous efforts to combat TB treatment interruption. In parallel with the defaulter tracing system, Directly Observed Treatment, Short-course (DOTS) has been a global core strategy to increase treatment adherence since 1993 (Maher, 2009; World Health Organization, 2017). On top of fee exemption for the anti-TB drug in most developing countries, fixed-dose combination tablets for tuberculosis treatment have been advocated since the 1980s, primarily to ensure optimal adherence (World Health Organization, 1999). Notwithstanding the established policy and legislative framework intended to optimise acceptance and access to treatment, TB treatment interruption remains a global public health challenge across nations particularly in high disease burden countries (Sabate, 2003; World Health Organization, 2017). In developing and high TB burden countries, TB treatment interruption has been reported ranging from 6 to 30% (Connolly et al., 1999; Dodor, 2004; Kliiman & Altraja, 2010).

Previous studies delineated risk factors of TB treatment interruption. These include younger age, male, low educational level, unemployment, being immigrant and HIV infection, which had significantly influenced TB treatment default (Chee et al., 2000;

Connolly et al., 1999; da Silva Garrido et al., 2012; Kliiman & Altraja, 2010; Millet et al., 2009; Naing et al., 2001; Tachfouti et al., 2013). Meanwhile, smoking and alcoholism have been consistently reported as the risk factors of TB treatment interruption (Bagchi et al., 2010; Chandrasekaran et al., 2005; Kliiman & Altraja, 2010; Sulaiman, & Ali, 2010; Vijay et al., 2010).

In the recent years, the outstandingly high burden due to TB treatment interruption has resulted in major awareness about the importance of assessing the timing of interruptions and determinants of the interruptions at different stages of the treatment course (Kruk et al., 2008). While much has been elicited on the determinants of TB treatment interruption, to the best of our knowledge there has been a scarce systematic review on the timing of interruption and prognostic factors contributing to different timing of treatment interruption. In addition, there are a number of prognostic factors reported previously, but few had been consistently identified from one study to another (Jenkins et al., 2013; Jepchumba et al., 2017; Akessa et al., 2015). Therefore, this review aims to examine evidence from published literature on the timing of TB treatment interruption in TB treatment, and subsequently to assess prognostic factors of TB treatment interruption at different time points of the treatment course. The duration information from survival analysis is fundamental to assist in designing time relevant intervention strategies in TB case holding and management, at which a different timeline of impactful adherence strategy can be planned accordingly.

METHODS

Data Sources and Literature Search Strategy

Literature search was systematically conducted via three electronic databases, namely *PubMed, Scopus*, and *ScienceDirect* in February 2018. The *Pubmed* search terms were ("survival"[MeSHTerms] OR ("survival"[All Fields] OR "survival time"[MeSHTerms]) OR ("survival time"[AllFields]) OR ("time*"[MesHTerms]) OR ("time*"[AllFields]) AND ("tuberculosis"[MeSHTerms] OR "tuberculosis"[AllFields]) AND ("treatment interruption"[MeSHTerms] OR "treatment interruption"[AllFields] OR ("treatment default"[MeSHTerms]OR "treatment default"[AllFields] OR ("default"[MeSHTerms]OR "default"[AllFields]). A similar search strategy was adapted in order to search for articles from *ScienceDirect*, and *Scopus*. The search for scholarly literature was also extended to *Google Scholar.*

All retrieved abstracts and titles were read and screened by three independent investigators (Q.S, S.M.S, and L.P.Y). The inclusion criteria were; original studies in English language, cohort studies of patients with tuberculosis, studies with TB treatment interruption reported as the primary outcome, as well as papers presenting any temporal data on TB treatment interruption such as mean/median time to default, survival probability, cumulative hazard or hazard function. In terms of TB treatment interruption, a variety of

criteria for defining interruption was accepted (for example early treatment interruption, or interruption of two or more months). Due to the scarcity of relevant articles, the date range was expanded to include published articles in peer-reviewed journals from February 2003 to February 2018, instead of limiting the search only to the past 10 years. The types of papers excluded from the analysis were reviews or editorials, non-peer-reviewed review literature such as technical reports and web-based guidelines, articles focusing on unfavourable outcomes rather than TB treatment interruption, as well as articles describing temporal data without the assessment of prognostic factors. Full text of potentially eligible articles were retrieved and screened for eligibility, through which the discrepancies between the reviewers' preferences on potentially eligible articles were resolved.

Search Outcome

The search was electronically conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, 2009 (Moher et al., 2009). The PRISMA flow diagram for study selection is described in Figure 1. Firstly, 267 articles

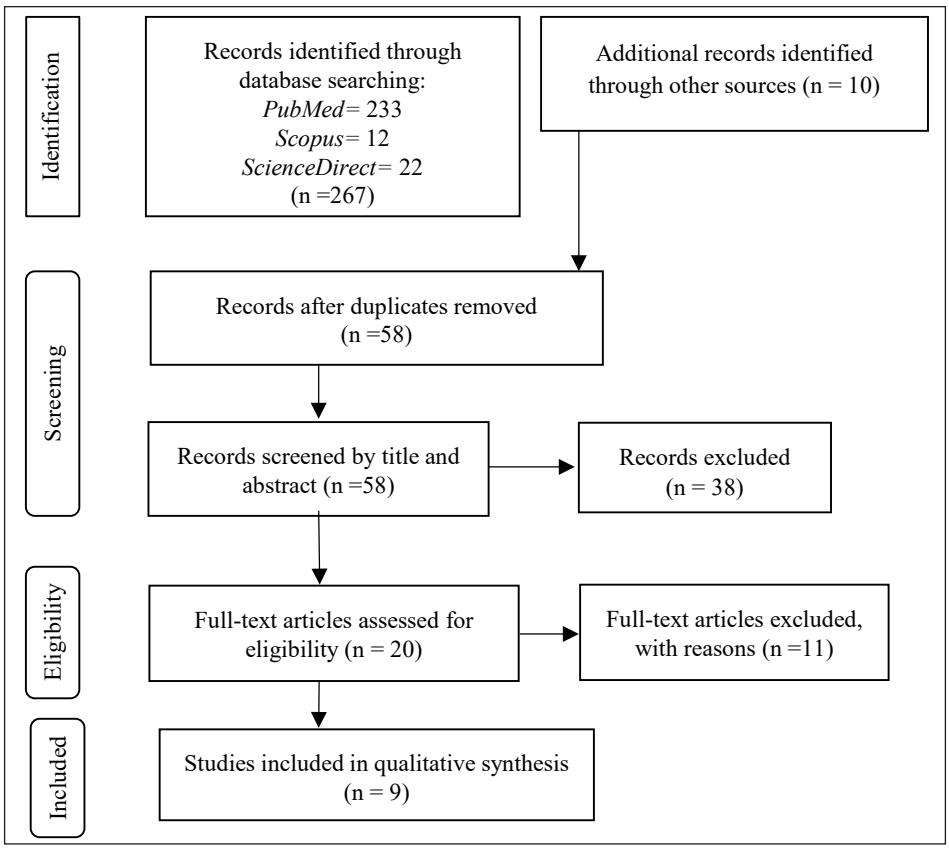

Figure 1. PRISMA flowchart for systematic search on timing and prognostic factors of TB treatment interruption

were identified from three databases. After excluding duplicated articles, assessment of titles and abstracts was executed, through which unrelated articles were omitted from further screening. After screening and looking for eligible articles based on the inclusion criteria, only 20 articles were examined. A sum of 11 articles were excluded due to the following reasons; articles focusing on unfavourable outcomes rather than TB treatment interruption or articles focusing on the survival time of treatment interruption without emphasizing prognostic factors.

Quality Assessment, Data Extraction and Data Analysis

The title, abstract and full text of every article retrieved from the search were screened by one reviewer (Q.S). To ensure rigour, a second set of reviewers (S.M.S and L.P.Y) were employed to assess the retrieved study for any doubt on the article's eligibility. The related articles were reviewed based on characteristics of the individual study including study details, exposure assessment, operational definition of treatment interruption, statistical method, as well as study outcomes including treatment interruption rate, survival time, survival probability and prognostic factors of TB treatment interruption. The included articles were evaluated for its risk of bias using Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2008). Assessment of bias was conducted based on six domains including the study's participants, study's attrition, prognostic factor measurement, outcome measurement, study confounding as well as statistical analysis and reporting. Some studies showed the lack of descriptions for prognostic factor measurement and study confounding particularly on the definition of prognostic factors, unclear methods for imputation of missing prognostic factors, as well as unclear description and measurement of important confounders. The list of studies is summarized in Table 1. Despite an overt criticism on the studies' quality and generalizability, it was not intended for article exclusion. Meanwhile, a meta-analysis of comparable studies was not conducted due to the presence of heterogeneity across the studies. Hence, a qualitative synthesis was performed.

RESULT

Finally, nine (9) eligible study articles were found to have met the predetermined study objectives and inclusion criteria. These articles were qualitatively synthesized, and the results were presented as follows.

Characteristic of Prognostic Studies

To date, several studies had been conducted to examine the time of TB treatment interruption and its prognostic factors. Most of the studies were designed as prospective cohort studies, and the majority of assessments were conducted in high TB burden countries. There had been a variation in the number of participants ranging from 249 to 90170 of patients

Table 1
Critical appraisal of prognostic studies on TB treatment interruption using quality in prognosis studies (QUIPS) tool

Study	Akessa et al. (2015)	Hill et al. (2005)	Jenkins et al. (2013)	Jepchumba et al. (2017)	Masini et al. (2016)	Pefura-Yone et al., (2014)	Rutherford et al. (2013)	Shargie & Lindtj (2007)	Sylvère (2015)
1. Study Participation: The study sample adequately represents the population of interest.									
Risk of bias	Low	Low	Moderate	Low	Low	Low	Low	Low	Moderate
2. Study Attrition: The study data available (i.e.,participants not lost to follow-up) adequately represent the study sample.									
Risk of bias	Low	Low	Moderate	Low	Low	Low	Low	Low	Moderate
3. Prognostic Factor Measurement: The PF is measured in a similar way for all participants.									
Risk of bias	Moderate	Low	Low	Low	Low	Low	Moderate	Low	Moderate
4. Outcome Measurement: The outcome of interest is measured in a similar way for all participants.									
Risk of bias	Low	Low	Low	Low	Low	Low	Low	Low	Low
5. Study Confounding: Important potential confounding factors are appropriately accounted for.									
Risk of bias	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate	Low
6. Statistical Analysis and Reporting: The statistical analysis is appropriate, and all primary outcomes are reported.									
Risk of bias	Low	Low	Low	Low	Low	Low	Low	Low	Low

seeking treatments from both hospitals and health clinics. Most of the participants were from the middle-age group. In term of exposure assessment, there had been prominent diversity across the studies. Most of the studies evaluated the demography of the patients, organizational factors as well as biomedical assessments such as comorbidities and treatment-related factors, but a limited assessment was made in cognitive, behavioural and psychosocial aspects. The characteristics of the individual study are described in Table 2.

With the exemption of two studies conducted by Hill et al. (2005) and Masini et al. (2016), most of the studies had computed Cox Proportional Hazard in analysing time to event data. Due to violated proportionality assumption for the Cox regression, Hill et al. (2005) computed the Extended Cox Regression in his assessment. Meanwhile, Masini et al. (2016) incorporated both fixed effects and accounted for the geographic region of Kenya via a random effect's component, hence mixed effect Cox proportional hazard modelling was computed.

TB Treatment Interruption

The burden of TB treatment interruption for the individual study is summarized in Table 3. In general, the proportion of TB treatment interruption ranged from 5.0 to 25.2%. The three highest treatment interruption burdens were recorded according to assessments across high TB burden countries (Hill et al., 2005; Pefura-Yone et al., 2014; Shargie & Lindtj, 2007). In addition, there was considerable variation in term of the definition of TB treatment interruption used in the studies. Instead of defining TB treatment interruption as two consecutive months of interruption, Rutherford et al. (2013) and Hill et al. (2005) used different operational definitions of interruption which were two consecutive weeks and three consecutive days of interruption respectively.

Survival Time, Survival Probability or Cumulative Hazard of TB Treatment Interruption

In this review, median survival time refers to length of time from either the date of diagnosis or treatment initiation, after which 50% of the TB patients are still in the treatment course, or have yet to develop TB treatment interruption (Kleinbaum, 1996). Meanwhile, survival probabilities or survival function is the probability that the individual survives from the date of diagnosis or treatment initiation, until the last day of treatment. To date, the median survival time and survival probability had been differently reported across the study locations, as presented in Table 3. Most of the studies revealed that the median time of TB treatment interruption was depicted during the maintenance phase of TB treatment (Akessa et al., 2015; Hill et al., 2005; Jenkins et al., 2013; Pefura-Yone et al., 2014). As opposed to the preceding findings, a prospective cohort study involving 264 of newly diagnosed PTB smear-positive patients in Bandung, Indonesia revealed that the median time to treatment

Table 2
Characteristics of studies included in systematic review

Author/Year	Study Design /Settings/ Study location	Participants	Exposure Assessment	Operational Definition of Treatment Interruption
Akessa et al. (2015)	Retrospective cohort, Jimma University Hospital, Ethiopia.	510 TB patients	Residential area, gender, sputum smear, type of TB, HIV test, and weight loss.	Those did not start treatments or treatment was interrupted for two consecutive months or more.
Hill et al. (2005)	Prospective cohort, urban public clinics in Greater Banjul, Gambia.	301 newly diagnosed TB patients	Age, gender, ethnicity, type of TB, employment status, family history, knowledge of the disease, perceived benefit, pre-treatment cost, travel distance, and financial stress.	Failure to present for DOTS for three consecutive days.
Jenkins et al. (2013)	Retrospective cohort, Moldova	4021 TB patients	Residential area, homeless, gender, nationality, occupation, salary, educational level, history of detention, household size, number of children, staying with TB patient, the degree of lung pathology, sputum smear, sputum culture, HIV status, drug resistance, and region of residency.	Treatment interruption occurred for two consecutive months and more.
Jepchumba, et al. (2017)	Prospective cohort, 25 public centres (private and public), Nairobi County Kenya	291 newly diagnosed, PTB smear-positive patients	Gender, age, the source of income, employment status, the frequency of wage payment, Educational level, alcohol consumption, DOTS staff sufficiency, and nature of the facility	TB patients who did not start treatments or treatments were interrupted for two consecutive months or more.
Masini et al. (2016)	Retrospective cohort, Kenya	90,170 TB patients	Patient type, TB type, gender, age, body mass index (BMI), HIV status, type of DOTS, employment sector, and nutritional support.	TB patients who did not start treatments after diagnosis, or treatment interruption for two consecutive months.
Pefura-Yone et al. (2014)	Retrospective cohort, Yaounde Jamot Hospital, Cameroon	1688 TB patients	Age, gender, residence, place of screening, the setting of intensive phase treatment, Type of TB, Type of patient, HIV serology, and sputum smear conversion.	Treatment interruption occurred for two consecutive months and more.
Rutherford et al. (2013)	Prospective cohort, community lung clinic, Indonesia	249 TB patients	Household head and household demographics, patient health, treatment-seeking behaviour, clinic accessibility, TB knowledge, social support, previous experiences with TB, perceived stigma and experience with clinic staff and facilities.	Primary default was defined as treatment discontinuation for more than 2 weeks. Permanent default was treatment interruption for two consecutive months and more.

Table 2 *(continue)*

Author/Year	Study Design /Settings/ Study location	Participants	Exposure Assessment	Operational Definition of Treatment Interruption
Shargie & Lindtj (2007)	Prospective cohort, Southern Ethiopia (hospital and health centre)	404 newly diagnosed PTB smear-positive patients	Gender, age, marital status, education, occupation, family size, monthly family income, duration of symptoms, residential area, the zone of residence, distance to diagnostic centre, and distance to a treatment centre.	PTB patients on treatments for at least four weeks and treatments were interrupted for more than eight consecutive weeks.
Sylvère (2015)	Prospective cohort, Benin, West Africa	1226 TB patients	Age, gender, nationality, sputum smear, TB history, a form of TB, HIV/AIDS infection, TB regime, and DOTS territory	Two consecutive months of treatment discontinuation.

Table 3
Systematic review of timing and prognostic factors of TB treatment interruption

Author/ Year	Statistical Method	Outcome		Prognostic Factors Identified		
		TB Treatment Interruption Rate	Survival Time and Survival Probability	Factors	Hazard Ratio	95% Confidence Interval
Akessa et al. (2015)	Cox proportional hazard regression analysis	13.5%	Median survival time was 5.7 months. The survival probability at the end of treatment was 85.5%.	Residential area (rural address)	4.393	1.58-12.18
Hill et al. (2005)	Extended Cox Proportional hazard analysis	25.2%	The median time of treatment interruption was 115 days (IQR=21-195).	0 to 90 days Perceived benefit (poor) After 90 days of treatment Travel distance	 3.64 2.67	 1.42–9.31 1.05–6.81
Jenkins et al. (2013)	Cox proportional hazard Regression	14.7%	The median time of default was 110 days for newly diagnosed TB patients.	Newly diagnosed cases Homeless Increase the educational level Living alone Destructive lung pathology HIV positive Presence of drug resistance Previously TB treated patients Living together with TB patient	 2.33 0.77 1.57 1.59 1.55 1.27 1.68 1.54	 1.64- 3.29 0.66- 0.91 1.20- 2.04 1.25-2.02 1.17- 2.05 1.10- 1.46 1.18-2.39 1.19-1.99

Table 3 *(continue)*

Author/ Year	Statistical Method	Outcome		Prognostic Factors Identified		
		TB Treatment Interruption Rate	Survival Time and Survival Probability	Factors	Hazard Ratio	95% Confidence Interval
Jepchumba et al. (2017)	Cox proportional hazard regression	6.5%	The median time of default was 56 days (IQR =36-105).	Type of health centre (public versus private)	0.210	0.05-0.95
				Adequate vs. Inadequate HCWs	0.195	0.07-.0.56
				Educational level (primary versus secondary)	5.28	1.18-23.59
Masini et al. (2016)	Mixed-effect cox proportional hazard modelling	4.5% for new patients	The hazard of treatment interruption was highest during the intensive phase.	Relapse cases	1.70	1.44–2.00
				Retreatment after failure	4.79	3.99–5.75
				Male	1.46	1.35–1.58
				Underweight versus normal	1.11	1.03–1.20
				Positive not on ART versus negative	1.96	1.70–2.26
Pefura-Yone et al. (2014)	Cox proportional hazard regression	20%	The median duration of treatment discontinuation was 90 days (IQR= 30-150).	Hospitalisation during the intensive phase	0.69	0.54-0.89
				Non-consenting for HIV screening	1.65	1.24-2.21
Rutherford, et al. (2013)	Cox proportional hazard regression	16%	The median time of default was 36 days (IQR= 7–99).	Liver disease	3.40	1.02-11.78
				Chest pain	2.25	1.06-4.77
				Night sweat	1.98	1.03-3.79
				Household wealth (poor)	4.24	1.12-16.09
				Walking to the clinic	4.53	1.39-14.71
				Low level of satisfaction with the clinic	3.85	1.17-12.62
Shargie & Lindtj (2007)	Cox proportional hazard regression	20%	The cumulative probability of default at the end of two months was 8.6%.	Distance from home to the treatment centre (>2 hours)	2.97	1.91-4.62
				Age (>25years)	1.71	1.09-2.68
Sylvère (2015)	Cox proportional hazard regression	5% for overall and 3% for intensive phase treatment interruption.	Median survival time was 2 months (IQR=1-3). The survival probability was 97.5% at 2 months and 94.9% at 6 months of treatment	Age	3.49	1.25-9.74
				HIV positive	3.82	2.28-6.41
				History of TB infection	0.13	0.03-0.53

interruption was 36 days (IQR=7–99) (Rutherford et al., 2013). Consistently, Masini et al. (2016) via a large retrospective cohort study involving 91099 TB patients in Kenya, had elicited evidence that the hazard rate of TB treatment interruption was highest during the intensive phase. Incongruent with preceding findings, Jepchumba et al. (2017) and Sylvère (2015) during their respective assessments at Kenya and West Africa, revealed that the median time of TB treatment interruption was towards the completion of the intensive phase.

Prognostic Factors In Terms of Time for TB Treatment Interruption

Prognostic factors in terms of time for TB treatment interruption elicited from the prognostic studies are presented in Table 3. These factors can be conveniently divided into socio-demographic and high-risk behaviours, clinical factors, health service factors as well as behavioural and cognitive factors.

Socio-demographic Factors and High-Risk Behaviour. In consistent with findings of Shargie and Lindtj (2007), and Sylvere (2015) demonstrated the prospective association between age and different time points of TB treatment interruption even though both had contradicting findings. Meanwhile, several other studies demonstrated that the age factor is an important confounder to be addressed during TB treatment interruption. Similarly, gender has also exerted confounding effect in most of the studies. Despite extensive evaluation of the demographic and socioeconomic profiling in most of the studies, there has been inconsistent findings across residential area, educational level, and family income. In the lens of high-risk behaviours, there is a limited evaluation of the smoking status, illegal drug use as well as alcohol consumption.

Clinical Characteristics. In this review, clinical parameters such as underlying disease, treatment-related factors, and comorbidity information were widely studied particularly in retrospective cohort studies. In essence, there have been consistent influences demonstrated by the type of TB patients and HIV infection on the time of TB treatment interruption, in which those with previous history of TB treatment and HIV positive status show higher probability of defaulting (Jenkins et al., 2013; Masini et al., 2016; Sylvere, 2015). In addition, there have been inconsistent findings in term of the history of hospitalization, body weight, symptoms improvement, sputum culture, chest x-ray grading as well as comorbidities.

Cognitive and Behavioural Factors. Despite limited assessment of cognitive and behavioural factors influence on the time of TB treatment interruption, Hill et al. (2005) evidently demonstrated that among 301 PTB patients in Gambia, those who were uncertain about the effectiveness of the standard treatment were 3.64 times at risk of developing

treatment interruption as compared to the reference group. However, this effect varied across the time, in which perceived benefits was the only exerting and significant effect on the time of TB treatment interruption in the first 90 days of the treatment course, but not thereafter. On the other hand, Rutherford et al. (2013) attempted a temporal assessment of TB knowledge and perceived stigma, but there were no significant influences to TB treatment interruption observed in terms of TB treatment interruption.

Health Service Factors. Health service factors such as staff adequacy, perceived access to healthcare centre and perceived patients' satisfaction have gained much interest from researchers during the assessment of the time of TB treatment interruption. It was evident in three distinct studies that health service access was found to have a significant association with different times of treatment interruption (Hill et al., 2005; Rutherford et al., 2013; Shargie & Lindtj, 2007). Earlier, Hill et al. (2005) in a prospective cohort study involving 301 TB patients in an urban community in Gambia, reported that patients with a travel time of more than half an hour or spent more than six *dalasis* (0.16 euro) for travel access had a higher risk of default, which was significantly observed after three months of treatment. In this study, the author postulated the correlation of built-up cost over time with a higher rate of defaulting during the maintenance phase. In contrast, a temporal assessment among 249 TB patients in Indonesia showed that travel time, travel distance (in kilometres) and travel cost did not influence TB treatment interruption significantly (Rutherford et al. (2013). Instead, patients who walked to the treatment centre had a higher risk of early treatment interruption, as the median time of default was 36 days. In the meantime, Shargie and Lindtj (2007) depicted that walking time of more than two hours posed a risk of maintenance phase treatment interruption in the rural community of Southern Ethiopia. The two latter studies shared a similarity, as both evaluated rural communities who predominantly walked to the treatment centres.

DISCUSSION

In this review, most of the studies shared several common characteristics, in which the selected studies were conducted in developing and high TB burden countries, and mean age of recruited participants was within the middle age group. However, quantitative analysis could not be performed due to limited finalized studies and considerable diversity across the studies, particularly on the study designs, duration of follow-up, as well as the operational definition of TB treatment interruption. Two studies did not explicitly report on the timing of default. Instead, the cumulative hazard risk or hazard functions were presented (Marsini et al., 2016; Shargie & Lindtj, 2007).

Notwithstanding the foregoing restriction, this review revealed that the timing of treatment interruption predominantly occurred during the maintenance phase. This finding

is incongruent with a previous systematic review conducted across the temporal data from developing countries which also demonstrated the maintenance phase as the point of exit from the treatment course (Kruk et al., 2008). In addition, this has been supported by previous qualitative studies whereby it was highlighted that most of the patients had significant symptoms improvement by the time they were in the maintenance phase (Martins et al., 2008; Widjanarko et al., 2009). Having said that, Rutherford et al. (2013) demonstrated that the median time of the TB treatment interruption was 36 days (IQR=7-99), whilst Masini et al. (2016) pointed out that the hazard rate of TB treatment interruption was highest during intensive phase, which collectively raised a postulation that additional effort for case holding relies on rigorous policy implementation and effectiveness of the existing programme in individual country to ensure adherence.

In the context of prognostic factors of TB treatment interruption, various factors contributing to TB treatment interruption at different time points have been identified. These factors are framed via socio-demographic and high-risk behaviour, clinical characteristics, health service factors as well as cognitive and behavioural factors. Prominently, travel distance and HIV infection were demonstrated as one of the prognostic factors of time to TB treatment interruption (Hill et al., 2005; Jenkins et al., 2013; Masini et al., 2016; Rutherford et al., 2013; Shargie & Lindtj, 2007; Sylvere, 2015). Undoubtedly, there are inconsistent findings, which largely influenced by study settings and study participants. Several studies included those with comorbidities such as HIV infection, liver disease, and diabetes which were predisposed to the complexity of treatment responses and standard care, thus influenced the mean time of duration of follow up. The comorbidities factors could also contribute to the competing risk of event occurrence, whereby this would lead to overestimation of the hazard of other factors.

Above all, findings from this review should be interpreted with caution. Firstly, this review was confined to published studies in which the generalizability of study population may render some restrictions. Crucially, the large heterogeneity was observed across the published studies particularly on study design, study participants and study population, duration of follow up, sample size and operational definition of TB treatment interruption. For example, there was considerable variation of TB treatment interruption rate, which strongly depending on the duration of follow up to allow sufficient event to be encountered, as well as the diversity of baseline characteristics of recruited participants. Therefore, a meta-analysis could not be performed to estimate the aggregate effect measure. In addition, this review included two studies dated more than 10 years. In this light, existing national programs and treatment protocol may have evolved and advances thereby impaired comparability of the studies.

Fundamentally, this review sheds light on the gap of individual research on longitudinal assessment of TB treatment interruption. It was demonstrated that most researchers focus

on demographic and biomedical context influences. While behavioural and psychosocial contexts have been echoed by WHO as a crucial aspect to be explored in TB treatment interruption, the prospective assessment of TB treatment interruption at different time points of the treatment course should emphasize on high risk behaviour, cognitive and behavioural aspect as well as psychosocial context which has been widely demonstrated in the literature as the determinants of TB treatment interruption (Sabate, 2003; World Health Organization, 1999). In addition, the assessment of events during the course of treatment, such as drug side effects and care provider-patient interactions, which could considerably influence a patient's decision to continue treatment, was not demonstrated in this review. This gap finding should be further explored, hence to endeavour a holistic assessment of health services factors which could influence TB treatment interruption. In terms of analysis, the quality of statistical reporting in future prognostic studies can be enhanced by subgroup analysis and by allowing a competing risks analysis of the hazard estimation in catering for diverse participants and organizational characteristics.

CONCLUSION

Although this review generally reveals that TB treatment interruption occurs more frequently during the maintenance phase, there has been a concomitant gap in understanding the prognostic factors of different time points of TB treatment interruption. The heterogeneity across the studies particularly on study design and operational definition of TB treatment interruption may limit solid inferences on the outcome measure, which requires further evaluation. In essence, health practitioners should integrate time-related information, while furthering suggestion that prognostic studies should incorporate assessments of cognitive, behavioural studies and psychosocial evaluation. The findings would be able to provide further evidence in framing future public health strategy.

ACKNOWLEDGMENT

The authors would like to thank the Director General of Health Malaysia for permission to publish this manuscript.

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